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RESEARCH ARTICLE

Diabetic autonomic neuropathy does not impede improvement in hypoglycaemia awareness in adults: Sub-study results from the HypoCOMPaSS trial

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Abstract

Aims: Impaired awareness of hypoglycaemia (IAH) increases the risk of severe hypoglycaemia in people with type 1 diabetes mellitus (T1DM). IAH can be reversed through meticulous avoidance of hypoglycaemia. Diabetic autonomic neuropathy (DAN) has been proposed as an underlying mechanism contributing to IAH; however, data are inconsistent. The aim of this study was to examine the effects of cardiac autonomic neuropathy (CAN) on IAH reversibility inT1DM.

Methods: Participants with T1DM and IAH (Gold score ≥4) recruited to the HypoCOMPaSS (24-week 2×2 factorial randomised controlled) trial were included. All underwent screening for cardiac autonomic function testing at baseline and received comparable education and support aimed at avoiding hypoglycaemia and improving hypoglycaemia awareness. Definite CAN was defined as the presence of ≥2 abnormal cardiac reflex tests. Participants were grouped according to their CAN status, and changes in Gold score were compared.

Results: Eighty-three participants (52 women [62.7%]) were included with mean age (SD) of 48 (12) years and mean HbA1c of 66 (13) mmol/mol (8.2 [3.3] %). The mean duration of T1DM was 29 (13) years. The prevalence of CAN was low with 5/83 (6%) participants having definite autonomic neuropathy with 11 (13%) classified with possible/early neuropathy. All participants, regardless of the autonomic function status, showed a mean improvement in Gold score of ≥1 (mean improvement −1.2 [95% CI −0.8, −1.6]; $p < 0.001$).

Conclusions: IAH can be improved in people with T1DM, and a long duration of disease, with and without cardiac autonomic dysfunction. These data suggest that CAN is not a prime driver for modulating IAH reversibility.

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KEYWORDS
cardiac autonomic neuropathy, diabetic autonomic neuropathy, impaired awareness of hypoglycaemia

1 | INTRODUCTION

Iatrogenic hypoglycaemia remains a major limiting factor[1] preventing people with type 1 diabetes (T1DM) from maintaining near normal plasma glucose. On average, a person with T1DM has two episodes of symptomatic hypoglycaemia/week and one or more episodes of severe hypoglycaemia (defined as cognitive impairment requiring third-party assistance)/year.[2] Hypoglycaemic events compromise both physiological counter-regulatory (CR) responses that would limit it, and behavioural defences against subsequent episodes.[3] A single episode of hypoglycaemia attenuates sympatho-adrenal responses to subsequent hypoglycaemia in healthy people[4] and in those with T1DM.[5,6] Hypoglycaemia of greater depth,[7] longer duration,[8] and higher frequency[9] results in greater attenuation of CR to subsequent hypoglycaemia.[10] This phenomenon reduces an individual's ability to perceive the onset of hypoglycaemia symptoms leading to impaired awareness of hypoglycaemia (IAH).[11]

Clinical IAH is heterogenous and progresses continuously, from intact hypoglycaemia responses to early loss of autonomic symptoms, reduced number and intensity, and rarely, total absence of symptoms.[12] Based on validated questionnaires, the reported prevalence of clinical IAH is ~25% in T1DM rising to ~50% after ≥25 years' treatment.[13–15] Meticulous avoidance of hypoglycaemia for as little as 2–3 weeks restores symptom awareness in many but adrenaline responses may not be restored in all, suggesting that sympatho-adrenal CR to hypoglycaemia remains persistently impaired in some individuals.[16–19]

Diabetic autonomic neuropathy (DAN) is a disorder of the autonomic nervous system presenting with a wide spectrum of symptoms affecting different organ systems. This serious microvascular complication of diabetes has been implicated in the pathogenesis of IAH. Several studies have suggested this link by showing that DAN increased the risk for severe hypoglycaemia (SH).[20,21] However, this link has been challenged by other data.[13,22,23] Moreover, while most studies investigating reversibility of IAH usually exclude DAN persons, some have showed that DAN appears to impede the reversal of IAH.[24]

DAN can affect several systems including gastrointestinal, genitourinary, sudomotor, and ocular systems, but cardiac autonomic neuropathy (CAN) is the most studied subgroup, perhaps due to its association with increased mortality.[25] The aim of our study was to investigate the relationship between CAN status and ability to successfully reverse IAH in a group of well phenotyped individuals with T1DM.

Novelty statement

What is already known?

- Impaired awareness of hypoglycaemia (IAH) significantly increases the risk of severe hypoglycaemia but can be reversed through avoidance of hypoglycaemia.
- Diabetic autonomic neuropathy (DAN) is hypothesised to be one of the underlying mechanisms but there is no proven link.

What this study has found?

- Prevalence of cardiac autonomic neuropathy (CAN) was low overall.
- Presence of CAN did not impede hypoglycaemia awareness improvement as participants with or without CAN improved their hypoglycaemia awareness.

What are the implications of this study?

- More research with larger numbers is required to elucidate pathophysiological defects culminating in IAH by addressing the challenge of clinical heterogeneity.

2 | METHODS

This sub-study was conducted as part of the larger HypoCOMPaSS (Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia) trial, a UK-based, multi-centred, prospective randomised controlled trial (RCT), the results of which have already been published.[26] The aim of HypoCOMPaSS was to optimise diabetes treatment in people with IAH to prevent biochemical hypoglycaemia and restore symptomatic awareness. Sheffield Teaching Hospitals was one of the five participating sites with another four in

Bournemouth (Royal Bournemouth Hospital), Cambridge (Addenbrooke's Hospital), Newcastle Upon Tyne (Newcastle Diabetes Centre), and Plymouth (Derriford Hospital).

The detailed protocol of the HypoCOMPaSS trial has been published.[27] Key inclusion criteria were people with T1DM aged 18–74 years with negative C-peptide levels (<50 pmol/L with a contemporaneous glucose >4 mmol/L), and IAH confirmed by a Gold score of ≥4. Key exclusion criteria were intolerance to insulin glargine and an inability to use or engage trial technology and self-monitoring requirements. Briefly, participants were randomly allocated to one of four treatment arms, stratified by baseline HbA1c (<64 and ≥64 mmol/L) and study centre; (1) multiple daily injections (MDI) with self-monitoring of blood glucose (SMBG), (2) MDI with SMBG and real-time continuous glucose monitoring (RT-CGM), (3) continuous subcutaneous insulin infusion (CSII) with SMBG and (4) CSII with SMBG and RT-CGM. All participants were treated for 24 weeks, during which insulin dose was titrated to avoid glucose levels <4 mmol/L as determined by RT-CGM and SMBG. All participants received standardised education face-to-face (individually/small groups), aimed to optimise hypoglycaemia recognition and to prevent significant events. The structured curriculum was designed to help individuals develop a personalised strategy for hypoglycaemia prevention without 'relaxing' overall glucose levels. It was one component of a multimodality intervention along with optimised glucose monitoring and insulin delivery. The episodes of SH were recorded prospectively by participants. The ability of participants to improve hypoglycaemia awareness was defined as the reduction of Gold score ≥1 as this degree of improvement has been linked to sustained reduction in SH[28]. Responders after completing the trial were defined as those with Gold score improvement to <4 while non-responders had a Gold score ≥4 after completing the trial intervention.

In this sub-study, detailed cardiac autonomic function testing was carried out during the 'wash-in period' of the trial prior to randomisation and intervention at all sites. The participants were grouped according to their cardiac autonomic status, and changes in Gold score were compared between baseline and 24 weeks.

2.1 | Cardiac autonomic function assessment

Cardiac autonomic functions were assessed through cardiovascular reflex tests ([1] heart rate response to deep breathing, [2] heart rate response to the Valsalva manoeuvre, [3] heart rate response to standing, and [4] systolic blood pressure response to standing). The cardiovascular reflex tests providing an objective diagnosis of abnormalities in the autonomic nervous system are non-invasive bedside tests.[29,30] The heart rate response to deep breathing was determined by calculating E/I ratio and a value of ≤1.00 was considered abnormal. For heart rate response to Valsalva, ratio of longest to shortest R-R interval was considered abnormal if ≤1.10. The heart rate response to standing was determined by calculating '30:15' ratio and was defined as abnormal if ≤1.00. Lastly, a drop of >30 mm Hg in systolic blood pressure on standing was considered abnormal. Participants were divided into three groups on the basis of the cardiovascular reflex tests according to a recent international consensus: normal (no abnormal test), early or possible (one abnormal test), and definite CAN (≥2 abnormal tests).[29] Orthostatic hypotension in addition to abnormal heart rate reflex test identifies more severe/advanced disease.

In addition to cardiovascular reflex tests heart rate variability (HRV), baroreflex sensitivity (BRS) tests were also performed (BRS performed at two centres because of logistical reasons [Sheffield and Newcastle]). For HRV and BRS, a five-minute electrocardiogram (ECG) recording was obtained with continuous blood pressure monitoring at rest. For HRV, the high-frequency (HF) band was defined as 0.15–0.4 Hz and the low-frequency (LF) band between 0.04–0.15 and LF norm was defined as the ratio between LF and total power.

To ensure the tests were not influenced by external factors, participants were asked to refrain from smoking and caffeine on the test day. Beta blockers were discontinued 48 h before autonomic function testing. A period of 3 min rest preceded each test, and all tests were carried out in a dark and quiet room. The testing was completed at each site using local equipment.

2.2 | Statistics and analysis

Data that followed an approximate normal distribution were summarised using mean and standard deviation (SD) and skewed data were summarised using median and interquartile range (IQR). Spectral HRV parameters were logarithmically transformed to approximate a normal distribution. Patterns in the change in Gold score and diabetes duration by CAN category were explored using boxplots. The associations between prevalence of CAN and change in Gold score between groups were assessed using Chi-square test for independence. Following the 24-week RCT, a comparison of baseline and follow-up data was completed using a paired t test. Statistical analysis was performed with SPSS (version 25.0, IBM, Chicago, Illinois). A p-value ≤0.05 was deemed statistically significant.

2.3 | Ethics

Ethical approval for this study was obtained from the Yorkshire and Humber Research Ethics Committee (12/YH/0035) while the local approval was granted by Sheffield Teaching Hospitals NHS Foundation Trust (STH16283/CSP94410). The main HypoCOMPaSS trial was approved by Sunderland Research Ethics Committee and Clinical Trial Authorisation was given by the Medicines and Healthcare products Regulatory Agency (17136/0246/001-0001).

3 | RESULTS

A total of 110 participants with IAH (Gold score ≥4) were recruited to the main HypoCOMPaSS trial; 6 participants were excluded because of elevated C-peptide levels and 8 withdrew from the study before randomisation. Ninety-six were randomised, all with C-peptide negative T1DM (<50 pmol/L in all except 2: 87; 103 pmol/L). Of these, a further 13 were excluded because of failure to complete the 6-month treatment period (9), or complete end of study questionnaires including Gold score assessment, and incomplete cardiac autonomic function testing, both key parameters for our sub-study (4). Thus, a total of 83 participants were included.

3.1 | Baseline characteristics

The incidence of SH was high with a mean rate 9 (13) episodes in the 12 months prior to the study (median 4 [2.5]; range 0 to >50 episodes). Eight participants reported no SH episodes in the year prior to the study and five reported greater than 50 episodes in the previous 12 months. All participants underwent detailed cardiac autonomic function testing. The baseline characteristics and cardiac autonomic function tests of the final 83 participants are shown in Table 1.

TABLE 1 Baseline characteristics and cardiac autonomic function tests of participants included in sub-analysis.

Baseline characteristics		*n*
Age, years	48 (12)	83
Female sex, *n*	52 (63%)	83
BMI, kg/m^2	27 (5)	83
Duration of diabetes, years	29 (13)	83
HbA1c		
mmol/mol	66 (13)	83
%	8.2 (3.3)	
Insulin dose, units/kg	0.65 (0.25)	82[a]
Gold score	5 (1)	83
SH in the last 6 months	1.0 [2.5]	83
SH in the last 12 months	3.5 [6.5]	83
HR, bpm	72 (10)	83
Systolic blood pressure, mmHg	131 (19)	83
Diastolic blood pressure, mmHg	76 (11)	83
Retinopathy	52 (63%)	83
Peripheral neuropathy	14 (17%)	83
Nephropathy	3 (4%)	83
Macrovascular disease	11 (13%)	83
HRV and BRS		
SDRR	34 (20)	83
RMSSD	23 (20)	83
Log LF	2.23 (0.66)	83
Log HF	1.91 (0.63)	83
BRS ($n=32$)	10.3 (5.4)	83
Abnormal BRS	10 (12%)	32[b]
Cardiac autonomic function status		
Normal cardiac autonomic function	67 (81%)	83
Possible/early DAN	11 (13%)	83
Definite DAN	4 (5%)	83
Definite DAN with orthostatic hypotension	1 (1%)	83

Note: Data are given as mean (SD), median [IQR] and actual number (%).

Abbreviations: BMI, Body mass index; BRS, Baroreflex sensitivity; DAN, Diabetic autonomic neuropathy; HF, High frequency spectral power; HR, Heart rate; LF, Low frequency spectral power; RMSSD, Root mean square of difference in successive RR intervals; SDRR, Standard deviation of RR intervals; SH, Severe hypoglycaemia.

[a]Dose not available.

[b]BRS only performed in two study centres.

3.2 | Hypoglycaemia awareness improvement

The results of the HypoCOMPaSS trial have been published in full.[26] The population in this sub-analysis also showed similar improvements in hypoglycaemia awareness. The annualised SH rate reduced by more than five-fold with only 6% participants experiencing SH at the end of the trial compared with 92% at the start. This reduction was associated with reductions in insulin dosages but without a deterioration in overall glycaemic control. Gold score improved significantly in the overall study population between baseline and 24 weeks (Table 2).

3.3 | Cardiac autonomic neuropathy and hypoglycaemia awareness improvement

In the group with no CAN, the mean Gold score improved from 5.2 to 4.1 after trial intervention. While in early/possible and definite CAN groups, the mean Gold score improved from 5.5 to 4.1 ($p<0.001$), and 5.0 to 4.0 ($p<0.001$)

at 24 months, respectively. The presence of CAN did not impede the ability of participants to improve hypoglycaemia awareness (Gold score reduction ≥1). 43/67 (64%) of participants without CAN improved their Gold score, while 8/11 (73%) and 3/5 (60%) in early/possible and definite CAN groups improved their Gold score after intervention in the trial. A Chi-square test for independence indicated no significant association between cardiac autonomic function status and a reduction in Gold score of ≥1 ($p = 0.743$). The mean reduction in Gold score was −1.2 (95% CI −0.8, −1.6; $p < 0.001$). The greatest reduction was seen in participants with early CAN with a mean reduction of −1.4 (95% CI −0.4, −2.4), $p = 0.01$ and the smallest reduction was seen in participants with definite CAN −1.0 (95% CI 0.8, −2.8; $p = 0.18$). Participants that had normal cardiac autonomic function had a mean reduction in Gold score of −1.2 (95% CI −0.8, −1.6; $p < 0.001$) (Figure 1). Participants with both normal BRS ($n = 22$) and abnormal BRS ($n = 10$) showed reductions in Gold score of −0.9 (95% CI −0.2, −1.7; $p = 0.02$) and −1.2 (95% CI −0.7, −1.6; $p < 0.001$), respectively.

The duration of diabetes in participants with definite or possible CAN was 31.9 ± 9.6 years compared with 28.0 ± 13.3 years in participants with no CAN; however, this difference was not statistically significant ($p = 0.27$ [paired t-test]). The duration of diabetes also did not influence the recovery of IAH among each group (Figure 2).

TABLE 2 Severe hypoglycaemia, hypoglycaemia awareness, HbA1c and insulin doses in study population at baseline and 24 weekend point.

	Baseline	Week 24	*p*-value	*n*
SH				
Annualised rate	8.8 (13.4)	1.6 (6.2)	<0.001	83
	3.5 [6.5]	0.0 [0.0]		
Proportion affected	92%	6%		
Gold score	5.3 (0.9)	4.1 (1.6)	<0.001	83
	5.0 [1.0]	4.0 [2.0]		
HbA1c				
mmol/mol	66 (13)	66 (11)	0.404	78
%	8.2 (3.3)	8.2 (3.2)		
Insulin, units per kg	0.65 (0.25)	0.53 (0.17)	<0.001	78

Note: Data are mean (SD) and median [IQR].

Abbreviation: SH, severe hypoglycaemia.

4 | DISCUSSION

Our findings demonstrate that IAH can improve in people with T1DM and a long duration of disease, with and without cardiac autonomic neuropathy, indicating that autonomic neuropathy may not be a prime driver in modulating reversibility of IAH. Notwithstanding, the low incidence of CAN at baseline, these data also suggest that IAH may not be a major contributor to the pathophysiology of IAH.

The prevalence of CAN was relatively low in our study (6%). The most commonly reported data evaluating the prevalence of CAN are from the Diabetes Control and Complications Trial (DCCT)[31] and its follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC).[32] In the DCCT, which recruited participants with a duration of T1DM of between 1 and 15 years, prevalence of CAN was 9%. This rose to 31% during EDIC, where researchers followed up 90% of participants from the DCCT with a duration of diabetes greater than 15 years. The low prevalence in our study may be because the prevalence of CAN varies depending on the cohort of participants recruited, tests used, and the definition of CAN in each study. In the above mentioned two studies, CAN was defined as an abnormality in either heart rate variability during deep breathing with the

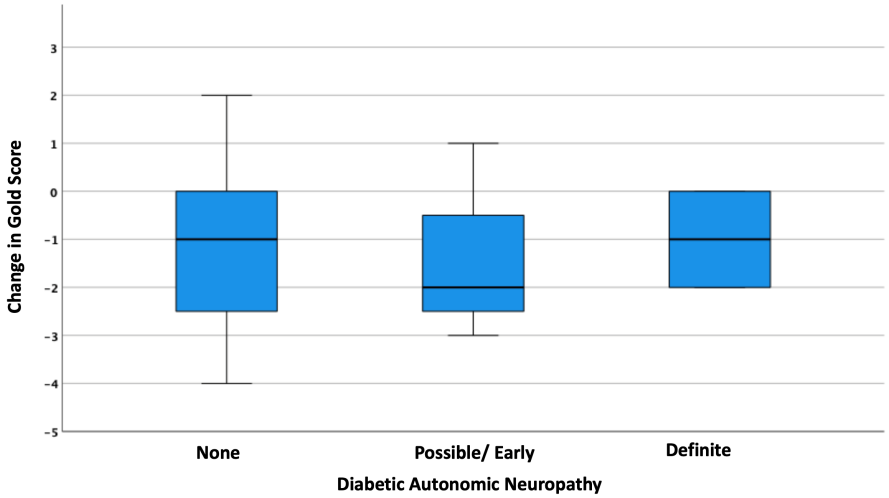

FIGURE 1 Effect of cardiac autonomic status on improvement of Gold score (Each box delineates inter-quartile range, central line shows median and whiskers mark minimum and maximum values).

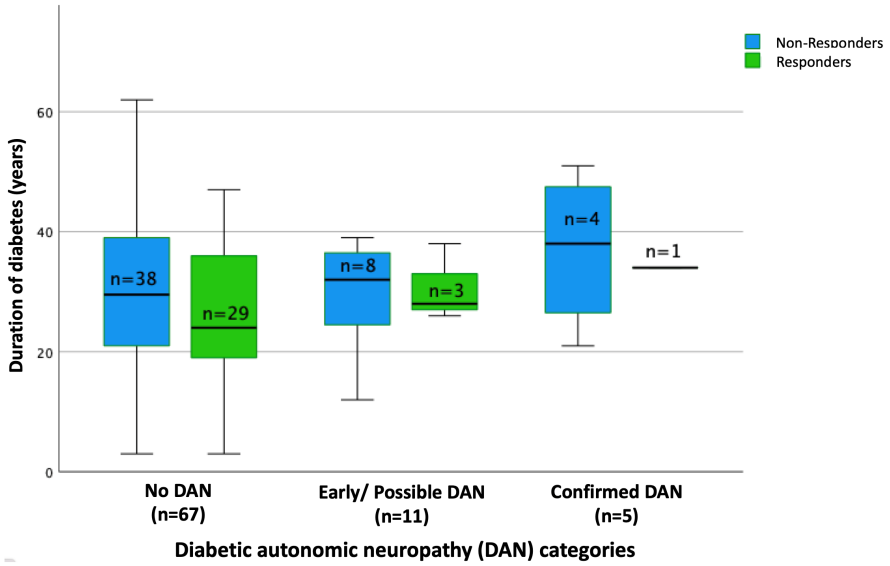

FIGURE 2 Relationship of IAH reversal with duration of diabetes in all DAN groups (Each box delineates inter-quartile range, central line shows median and whiskers mark minimum and maximum values).

Valsalva manoeuvre, or drop in diastolic blood pressure on standing. Applying these diagnostic criteria to participants in our study, 19% will be classified as having CAN. Furthermore, in DCCT and EDIC, age-related normal ranges for cardiac reflex tests were not used unlike our study which may also account for the reduction in CAN prevalence in our data.

Recurrent episodes of hypoglycaemia lead to decreased sympatho-adrenal responses, which, in some, results in IAH.[4–6] Frequent hypoglycaemic episodes attenuate the CR response to future hypoglycaemia by lowering the glycaemic threshold to activate the sympatho-adrenal response.[4,33] This can lead to a vicious cycle of repeated episodes resulting in further blunting of CR (predominantly adrenergic) responses. This phenomenon has been previously termed 'hypoglycaemia-associated autonomic failure' (HAAF)[34] but is a dynamic functional disorder that is clearly distinct from classical DAN,[1,33] a serious neuropathic complication of diabetes. Whilst there is no failure of the autonomic system in HAAF, an attenuated sympatho-adrenal response to a given level of hypoglycaemia, a key feature of hypoglycaemia-associated autonomic failure, is common with DAN.[21,35,36] The term HAAF can thus be misinterpreted to suggest that DAN could be its underlying cause. However, since structural autonomic neuropathy is generally only observed in individuals with a long duration of diabetes, the prevalence of IAH as well as DAN increases with diabetes duration.[37] This makes diabetes duration an important potential confounder in studies investigating the relationship between IAH and DAN. In our study, we analysed hypoglycaemia awareness improvement in responders and non-responders examining the impact of diabetes duration with further stratification by CAN status (Figure 2). Although diabetes duration in responders was less than that of non-responders, this difference was not statistically significant. This could, however, be to the result of a small sample size and hence limited power. However, findings from a recent study[23] have also demonstrated that in people with normal and impaired awareness ($n = 33$ in each group, median [IQR] diabetes duration 31 [13.5] vs. 30 [13.5] years), there was no difference in the prevalence of DAN between the groups.[23]

Our data thus argue against a causal link between CAN and IAH, and the underlying mechanisms for IAH remain to be elucidated. It has been proposed that IAH stems from a central maladaptive response in brain that follows frequent hypoglycaemia.[33,38] CR failure in hypoglycaemia has been extensively studied in the hypothalamus,[39] but other brain regions may also be involved.[40] Recent neuroimaging data have revealed activation of interconnected brain regions related to arousal, decision making, and reward during hypoglycaemia, indicating disruptions in neural pathways affecting recognition and management of hypoglycaemia.[41] Restoring awareness through structured education and sensor-augmented pump therapy increased blood flow in self-awareness and decision making pathways, but arousal and emotional processing remained less responsive.[42] These changes may impede effective hypoglycaemia management and contribute to persistent IAH in a vulnerable group. A previous analysis of the HypoCOMPaSS cohort supported an as yet unexplained neurological impairment in participants who did not recover sufficient hypoglycaemia awareness to absolutely prevent further severe hypoglycaemia over 24 months following initial trial intervention.[43] These partial responders had an 8-fold higher incidence of peripheral neuropathy compared with complete responders (39.3% vs. 4.7%). Despite the proposed potential neurological

basis for IAH, our findings and that of other studies suggest a mechanism that is distinct from DAN.[23]

One strength of our study is that unlike most IAH reversal or hypoglycaemia awareness improvement studies, we did not exclude participants with autonomic neuropathy and carefully phenotyped them in a relatively large cohort of individuals in an RCT setting. Further, our analyses have considered potential confounding from diabetes duration. To our knowledge, two other studies[24,44] have studied participants with DAN and IAH. In an older study,[24] a 6-month treatment period to avoid biochemical hypoglycaemia in those with T1DM and CAN was followed by hypoglycaemic clamps demonstrating an improvement in both symptomatic and adrenergic responses in participants with and without CAN. Awareness status in this study was not established using Gold or Clarke scores which is a limitation. Whilst our analyses are limited to the Gold score alone, this is widely accepted as a validated method for IAH stratification because of its well-established association with severe hypoglycaemia[45] as well as counter-regulatory responses during clamp studies.[46] In a more recent study by Kamel et al.,[44] a small number ($n = 5$) displayed improved hypoglycaemia awareness despite abnormal cardiac autonomic function tests. However, in this study, the reversal of IAH was achieved via either islet cell or whole pancreas transplants. Overall, both studies broadly support our findings but within the caveats of their own methodology and limitations.

A key limitation of our data is the low prevalence of participants with definite CAN which means that our study could be underpowered. This sub-study is a secondary analysis of the existing HypoCOMPaSS trial dataset, in which we used all participants eligible for this sub-analysis, and therefore an a priori power calculation was not performed. Participants from the HypoCOMPaSS trial who did not complete their treatment period, were excluded in this sub-study and their data were not available for comparative analysis, to assess if they meaningfully differed from the included study participants. Other measures of autonomic dysfunction including tests of pupillomotor or sudomotor function were not performed. Furthermore, the participants were investigated by different clinical teams in different parts of the country, so it is possible that inter-investigator differences may have led to inconsistency in the measurements of cardiac autonomic tests. A further limitation is that BRS was done only at two centres and data on autonomic function testing was confined to cardiac reflex testing only.

We conclude that CAN is not a prime driver of IAH as its presence does not appear to impede successful recovery of IAH. Further mechanistic research in larger numbers is needed to understand to what extent factors such age, sex, duration of diabetes, diabetes complications, residual C-peptide levels, recent severe hypoglycaemia and antecedent hypoglycaemia predict an individuals' ability to regain awareness following intervention. This is crucial, since different pathophysiological defects causing IAH may respond differently to clinical interventions and there is a need for better understanding of underlying neurological mechanisms and identification of biomarkers that can predict treatment response and enable an individualised approach to successful management of this debilitating consequence of exogenous insulin replacement. This may include earlier consideration of beta-cell replacement therapy in those unlikely to respond to hypoglycaemia avoidance through conventional medical management alone.[47] The lower-than-expected prevalence of CAN in our study also calls for contemporary epidemiological studies to establish the prevalence of CAN in T1DM with a short and long duration of disease.

AUTHOR CONTRIBUTION

M.F.A. and E.W. co-analysed data and co-wrote the first draft of the manuscript. E.W. and A.L.S. recruited participants. A.I. developed the methodology, reviewed data, guided further analysis, edited the manuscript and led on contributing to the discussion. A.B. and I.R. provided statistical support. S.A.L., J.A.M.S. and S.R.H. designed the study, and contributed to the discussion. All authors provided critical input on multiple versions of the manuscript. All authors approved the final submitted version. A.I. is the guarantor of this work, and as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis.

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CONFLICT OF INTEREST STATEMENT

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